Percutaneous pulmonary artery biodegradable stent: a new armament to fight pulmonary artery stenosis?

Hai Zou, Sheng-Qing Li

Department of Respiratory Medicine, Huashan Hospital, Fudan University, Shanghai 200040, China.

To the Editor: Pulmonary artery stenosis can be caused by numerous factors, such as tetralogy of Fallot, pulmonary atresia, tricuspid atresia with pulmonary artery stenosis, atresia combined with another congenital heart disease and pulmonary circulation dysplasia,[1,2] William syndrome, and Alagille syndrome. Additionally, pulmonary artery branch stenosis can be the consequence of some genetic metabolic diseases, such as congenital rubella.[3] Most cases of pulmonary stenosis require surgical intervention.

Conventional surgical angioplasty of pulmonary artery necessitates cardiopulmonary bypass, which has a negative impact on the child's cardiopulmonary function. In addition, the surgical protocol requires the dissociation of the distal branch of the pulmonary artery. This procedure causes significant trauma and often fails to dissociate the culprit lesion, ultimately resulting in an unsuccessful operation. Therefore, traditional surgical procedures are ineffective for distal pulmonary artery stenosis or long tubular stenosis and are associated with a high probability of restenosis. Over the past 30 years, stent implantation for pulmonary artery stenosis has developed rapidly and has become the preferred treatment method.[4,5] In adults and older children with simple pulmonary artery stenosis, percutaneous stent implantation via femoral vein is often selected to relieve pulmonary artery stenosis while avoiding thoracotomy. This procedure is widely accepted because it minimizes the trauma, and ensures fast recovery, good therapeutic outcome, and low rate of restenosis.[6] Currently, the main metallic materials used for stent manufacturing are stainless steel, platinum-iridium alloy, tantalum, titanium, nickel-titanium alloy, and cobalt-chromium alloy.

According to the method by which the stents are deployed, they can be categorized into self-expanding and balloon-expandable stents. Self-expanding devices are made mostly of super-elastic nickel-titanium alloys, which can recover to their original shape after deployment. During its delivery to the lesion site, the stent can be enclosed in a small transport sheath so that it can pass easily tortuous vessels. It is also suitable for use in longer vascular lesions. However, due to the limited mechanical strength of the nickel-titanium alloy, it is seldom used in the treatment of pulmonary artery branch stenosis after the surgery for congenital heart disease.

Currently, pulmonary artery stents are used clinically in the following cases: (1) In patients with simple pulmonary artery stenosis to relieve pulmonary artery stenosis without performing thoracotomy; (2) In patients with cardiac malformations, as a part of surgical mosaic therapy, such as the percutaneous implantation of pulmonary artery stent for residual pulmonary artery branch stenosis in the tetralogy of Fallot; and (3) As a palliative treatment, that is, in cases of a narrow external canal from right ventricular outflow tract to the pulmonary artery, stent implantation can extend the lifespan of the external canal, eliminating the need for a cardiopulmonary bypass and reducing the surgical trauma in children.

Drug-eluting stents (DESs) release factors inhibiting the excessive proliferation of neointimal cells, thereby reducing the incidence of restenosis.[7] Rapamycin-eluting stents from Cypher, and paclitaxel-eluting stents from Cordis (Marlborough, MA) and Boston Scientific (Marlborough, MA) were milestones in the history of percutaneous transluminal coronary interventions. However, the use of non-biodegradable DES can result in cause delayed endothelialization, in-stent thrombosis, poor long-term stent adherence, aneurysms at stent sites, inflammation, and polymer-induced allergic reactions. These adverse effects lead to restenosis in some patients, and revascularization is required.

To solve these problems, biodegradable stents have been developed. To ensure optimal performance of the stent, biodegradable materials needed to be designed and

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001061

Correspondence to: Prof. Sheng-Qing Li, No. 12 middle Urumqi Road, Jing'an District, Shanghai 200040, China
E-Mail: shengqingli9655@163.com

Chinese Medical Journal 2020;133(19)

Received: 04-04-2020 **Edited by:** Ning-Ning Wang

developed. These materials should be susceptible to hydrolysis and degradation in the presence of tissue fluids, various enzymes secreted by the cells, so that they could be eventually decomposed into short polymers and small molecules, and absorbed by the organism. However, the degradation products could enter the metabolic system of the body, or induce the growth of specific cells triggering the formation of new tissue. Thus, the ideal pulmonary artery biodegradable stent should have the following characteristics: (1) good histocompatibility; (2) ability to provide adequate mechanical support early after implantation; (3) biodegradability with the degradation products being harmless to the body; and (4) ability to carry more anti-proliferative drugs than the metal stent and slowly release them locally. At present, based on the material used, biodegradable stents can be divided into two types: polymer and metal. A large variety of stents are made of polymers; poly-L-lactic acid is and commonly used. However, the mechanical strength of polymer stents is poor, necessitating an increased thickness of the stents to compensate for this deficiency, thus limiting their application in small-diameter vessels. In addition, by-products released after degradation of these stents, such as catalysts and solvents, are harmful to tissues and may trigger local inflammation. Finally, the degradation rate of polymer stents is slow and the incidence of restenosis rate is high.

Degradable metallic materials are generally composed of iron and magnesium. Recently, zinc has also shown great potential in the fabrication of degradable stents.[8] In comparison with polymer stents, metal-based biodegradable stents have several advantages: (1) Sufficient strength of support, particularly relevant in narrow blood vessels; (2) Iron and magnesium, the two main components of metal stents released during degradation, are not toxic to the human body; (3) Rapid degradation preventing the side effects of the prolonged presence of a foreign body in the blood vessel, such as inflammation or thrombosis; (4) The ability of oxidative metabolites of iron to inhibit neointimal hyperplasia and thrombosis, and acceleration of intimal formation by metabolites of magnesium, as demonstrated in animal studies; and (5) The implantation of biodegradable stents may induce remodeling of stenosed vessels spontaneous development of new vessels.

Degradable stents have many clinical applications. (1) Establishment of a biologic conduit from the right ventricular outflow tract to the extrapulmonary duct. Based on a retrospective study with a 10 years follow-up, Aggarwal and co-workers[9] concluded that the implantation of degradable stents is effective in the treatment of stenosis or restenosis of the right ventricular extrapulmonary duct. (2) Treatment of pulmonary artery branch stenosis. Stent implantation for the treatment of pulmonary artery branch stenosis in patients with congenital heart disease was first reported in the 1980s and is currently widely accepted. (3) Internal and surgical mosaic therapy. Some cases of distal pulmonary artery stenosis may be associated with an unnecessary injury to the patients due to the inaccessibility of surgery or the need for cardiopulmonary bypass of extended duration. van Gameren and collaborators[10] treated congenital heart disease accompanied by peripheral vascular stenosis using a combination of trans-catheter intervention and surgery. This protocol was demonstrated to be an effective and safe way to treat complicated cases of congenital heart disease.

Alloy magnesium and magnesium alloys are biodegradable and absorbable, outperforming in this regard other traditional metallic materials. Moreover, they possess superior physical and mechanical properties, such as low density, high specific strength and specific stiffness, high flexural toughness, and are easy to process. Magnesium participates in multiple physiologic processes, but the small amounts that could be released from the stent will not cause damage to the human body. These advantages make magnesium-based biomaterials an attractive subject in the field of metal stents. Zartner and colleagues[11] reported for the first time the use of a degradable metal stent in a 26-week premature infant. Implantation of a magnesium alloy degradable stent was into the left pulmonary artery significantly improved its perfusion.

The most significant problem with magnesium alloy stents is their rapid rate of degradation by corrosion. As a result, they easily lose the ability to support blood vessels. The rapid corrosion of magnesium can also result in an increase of pH around implants, which may lead to alkali poisoning. Moreover, corrosion of magnesium can generate a large amount of H_2. Therefore, strategies for effective control of the rapid corrosion of magnesium alloy stents are urgently needed. Modifications of the stent surface are frequently used to control the corrosion rate of magnesium and its alloys; they include physical methods, chemical deposition, electrochemical deposition, and organic and polymer coatings. Among these methods, micro-arc oxidation is used most frequently. However, the coating obtained by a traditional micro-arc oxidation technology yields a rather porous structure, and the large size of the pores facilitates the corrosion of magnesium alloy by body fluids. In addition, long-term friction between micro-arc oxidation stent and blood vessel wall can cause inflammation and even restenosis. To counteract this phenomenon, vascular stents are designed to carry drugs, for example, rapamycin, L-ascorbic acid that, when released locally, inhibit excessive proliferation of neointima. However, at present, only one type of drug molecules can be incorporated in the stents for clinical use, restricting the possibility of achieving the desired effect. To compensate for the lack of resistance to corrosion of traditional micro-arc oxidation coatings, the current research efforts are focused on the preparation of multi-stage composite coatings on the magnesium alloy surface. However, only a few studies on the inhibition of restenosis by composite-coated DESs are available, and the specific mechanism of their action remains unclear.

Conflicts of interest

None.

References

1. Nielsen EA, Hjortdal VE. Surgically treated pulmonary stenosis: over 50 years of follow-up. Cardiol Young 2016;26:860–866. doi: 10.1017/S1047951115001158.

2. Gu Y, Jin M, Wang XF, Guo BJ, Ding WH, Wang ZY, *et al*. Balloon angioplasty as a modality to treat children with pulmonary stenosis secondary to complex congenital heart diseases. Chin Med J 2017;130:2793–2801. doi: 10.4103/0366-6999.215715.
3. Monge MC, Mainwaring RD, Sheikh AY, Punn R, Reddy VM, Hanley FL. Surgical reconstruction of peripheral pulmonary artery stenosis in Williams and Alagille syndromes. J Thorac Cardiovasc Surg 2013;145:476–481. doi: 10.1016/j.jtcvs.2012.09.102.
4. Cui KY, Lyu SZ, Zhang M, Song XT, Yuan F, Xu F. Drug-eluting balloon versus new-generation drug-eluting stent for the treatment of in-stent restenosis: an updated systematic review and meta-analysis. Chin Med J 2018;131:600–607. doi: 10.4103/0366-6999.226073.
5. Vida VL, Rito ML, Zucchetta F, Biffanti R, Padalino MA, Milanesi O, *et al*. Pulmonary artery branch stenosis in patients with congenital heart disease. J Card Surg 2013;28:439–445. doi: 10.1111/jocs.12121.
6. Niu JM, Zhang J, Qiu XJ, Wang J, Pei YH, Wang YL, *et al*. Comparison of clinical features and stent placement outcomes between airway stenosis caused by primary pulmonary malignancies and that caused by primary non-pulmonary malignancies. Chin Med J 2019;132:431–436. doi: 10.1097/CM9.0000000000000092.
7. Otsuka F, Byrne RA, Yahagi K, Mori H, Ladich E, Fowler DR, *et al*. Neoatherosclerosis: overview of histopathologic findings and implications for intravascular imaging assessment. Eur Heart J 2015;36:2147–2159. doi: 10.1093/eurheartj/ehv205.
8. Mostaed E, Sikora-Jasinska M, Drelich JW, Vedani M. Zinc-based alloys for degradable vascular stent applications. Acta Biomater 2018;71:1–23. doi: 10.1016/j.actbio.2018.03.005.
9. Aggarwal V, Dhillon GS, Penny DJ, Gowda ST, Qureshi AM. Drug-eluting stents compared with bare metal stents for stenting the ductus arteriosus in infants with ductal-dependent pulmonary blood flow. Am J Cardiol 2019;124:952–959. doi: 10.1016/j.amjcard.2019.06.014.
10. van Gameren M, Ligthart JM, Galema TW, Nieman K, Van Mieghem NM. Distinct pattern of constrictive remodeling in radiotherapy-induced coronary artery disease. JACC Cardiovasc Interv 2016;9:e121–e123. doi: 10.1016/j.jcin.2016.03.012.
11. Zartner P, Cesnjevar R, Singer H, Weyand M. First successful implantation of a biodegradable metal stent into the left pulmonary artery of a preterm baby. Catheter Cardiovasc Interv 2005;66:590–594. doi: 10.1002/ccd.20520.

How to cite this article: Zou H, Li SQ. Percutaneous pulmonary artery biodegradable stent: a new armament to fight pulmonary artery stenosis? Chin Med J 2020;133:2389–2391. doi: 10.1097/CM9.0000000000001061